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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/916,135	07/25/2001	Hajime Matsuzaki	3414	8220

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 12/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/916,135	MATSUZAKI ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2004* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,16-33 and 50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,16-33 and 50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Specification

1. The objection to the specification is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1, 16-18, 25-33 and 50 are rejected under 35 U.S.C. 102(b) as being anticipated by Shagin et al (Nucleic Acids Research (1999) 27(18) e23-25).

Shagin teaches a method of claims 1 and 50 comprising:

(a) fragmenting a first nucleic acid sample to produce fragments (see page ii, column 2, subheading "Model experiment", where lambda phage DNA was digested with HindII),

(b) ligating an adaptor to the fragments to generate adaptor ligated fragments (see page ii, column 2, subheading "Model experiment" where adaptors were ligated to the fragments),

wherein the 5' end of a first strand of an adaptor ligated fragment is complementary to the 3' end of said first strand and wherein the length of the complementary region is between 10 and 30 contiguous bases (see page ii, figure 1 and figure 2, panel A, where the adaptor has a 10 nucleotide self complementary region),

(c) generating a second nucleic acid sample by preferentially amplifying a plurality of the adaptor ligated fragments that are 400 to 800 base pairs in length by a polymerase chain reaction (see page ii, column 2, subheading "Model experiment", where lambda phage DNA was digested with HindII, which will result in 9 fragments between 400 to 800 basepairs, including the 728 basepair fragment from position 19842 to position 20569 of the Bacteriophage lambda sequence and the 574 basepair fragment from position 26745 to position 27318 of the Bacteriophage lambda sequence)

(d) wherein the concentration of PCR primer in the reaction is 0.4 to 0.8 micromolar (see page iii, figure 3, where 0.5 uM of the proximal primer was used),

and said reaction comprises a plurality of cycles wherein each of said cycles comprises a step of incubation at about 72 C for between 10 and 30 seconds (see page i, column 2, where the cycling protocol was for 18-22 cycles and included a step where the cycle was at 65 C for 20 seconds).

With regard to claims 16-18, Shagin teaches primers that are 22 nucleotides in length (see figure 2, panel A).

With regard to claims 25-26, Shagin teaches the use of HindII to cut the sample, which is a six base cutter (see page ii, column 2).

With regard to claim 27, Shagin teaches an adaptor which comprises the PCR primer template sequences (see page ii, fugre 2, panel A).

With regard to claims 28-32, Shagin teaches a sample where the second nucleic acid comprises at least 50% of the sample (see page i, column 1, for example).

With regard to claim 33, Shagin teaches the use of DNA and cDNA (see page i, column 1).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 20-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shagin et al (Nucleic Acids Research (1999) 27(18) e23-25) in view of Sorge et al (U.S. 2002/0119448 A1).

Shagin teaches a method of claims 1 and 50 comprising:

(a) fragmenting a first nucleic acid sample to produce fragments (see page ii, column 2, subheading "Model experiment", where lambda phage DNA was digested with HindII),

(b) ligating an adaptor to the fragments to generate adaptor ligated fragments (see page ii, column 2, subheading "Model experiment" where adaptors were ligated to the fragments),

wherein the 5' end of a first strand of an adaptor ligated fragment is complementary to the 3' end of said first strand and wherein the length of the complementary region is between 10 and 30 contiguous bases (see page ii, figure 1 and figure 2, panel A, where the adaptor has a 10 nucleotide self complementary region),

(c) generating a second nucleic acid sample by preferentially amplifying a plurality of the adaptor ligated fragments that are 400 to 800 base pairs in length by a polymerase chain reaction (see page ii, column 2, subheading "Model experiment", where lambda phage DNA was digested with HindII, which will result in 9 fragments between 400 to 800 basepairs, including the 728 basepair fragment from position 19842 to position 20569 of the Bacteriophage lambda sequence and the 574 basepair fragment from position 26745 to position 27318 of the Bacteriophage lambda sequence)

(d) wherein the concentration of PCR primer in the reaction is 0.4 to 0.8 micromolar (see page iii, figure 3, where 0.5 uM of the proximal primer was used),

and said reaction comprises a plurality of cycles wherein each of said cycles comprises a step of incubation at about 72 C for between 10 and 30 seconds (see page i, column 2, where the cycling protocol was for 18-22 cycles and included a step where the cycle was at 65 C for 20 seconds).

With regard to claims 16-18, Shagin teaches primers that are 22 nucleotides in length (see figure 2, panel A).

With regard to claims 25-26, Shagin teaches the use of HindII to cut the sample, which is a six base cutter (see page ii, column 2).

With regard to claim 27, Shagin teaches an adaptor which comprises the PCR primer template sequences (see page ii, fugre 2, panel A).

With regard to claims 28-32, Shagin teaches a sample where the second nucleic acid comprises at least 50% of the sample (see page i, column 1, for example).

With regard to claim 33, Shagin teaches the use of DNA and cDNA (see page i, column 1).

Shagin does not teach the use of ddNTPs in the PCR reaction or of exonucleases.

Sorge et al (U.S. 2002/0119448 A1) teaches that one way to limit enrichment to a selected area of a genome is by inclusion of a chosen concentration of chain terminating nucleotides such as dideoxynucleotides (see page 25, paragraph 369).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the nucleic acid selection method of Shagin et al as taught by Sorge et al (U.S. 2002/0119448 A1) publication which suggests using ddNTPs in limiting enrichment to selected regions since Sorge et al (U.S. 2002/0119448

A1) states "In order to generate an enriched subportion of the genome by this method, the extension must be limited to avoid the theoretical replication of the entire genome, which would not enrich for sequences near the sites recognized by the sequence-specific cleavage agent. One way to limit the length of the extension products is to include a chosen concentration of chain-terminating nucleotide analogs (such as dideoxynucleotides) to the extension mix (see page 25, paragraph 369)." An ordinary practitioner would have been motivated to modify the method of Shagin to use the dideoxynucleotides in order to achieve an enriched subportion of the genome, where necessary.

7. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shagin et al (Nucleic Acids Research (1999) 27(18) e23-25) in view of Sorge et al (U.S. Patent 5,556,772).

Shagin teaches and suggests the limitations of claims 1, 16-18, 25-33 and 50 as discussed above. Shagin does not teach the use of exonucleases.

Sorge teaches the addition of a polymerase with 3'-5' exonuclease activity to PCR reactions such as those of Shagin (see column 2, for example).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the nucleic acid selection method of Shagin et al as taught by Sorge et al (U.S. Patent 5,556,772) since Sorge notes "Prior to the inventors work, DNA synthesis in vitro was performed with a single purified DNA polymerase. In a variety of synthesis procedures, the subject compositions provide superior synthesis results, as compared with the synthesis results obtained with a single

DNA polymerase with less 3'-5' exonuclease activity than the enzyme with 3'-5' exonuclease activity alone (including synthesis results obtained with DNA polymerases that substantially lack 3'-5' exonuclease activity) (see column 3, lines 1-9)." So an ordinary practitioner would have been motivated to use the additional polymerase, with the 3'-5' exonuclease activity as taught by Sorge, in order to provide superior synthesis results as taught by Sorge in the PCR reaction.

8. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shagin et al (Nucleic Acids Research (1999) 27(18) e23-25) in view of Birkenmeyer et al (U.S. Patent 6,455,255).

Shagin teaches and suggests the limitations of claims 1, 16-18, 25-33 and 50 as discussed above. Shagin does not teach gel filtration of the adaptor ligated fragments.

Birkenmeyer recognizes a problem with the use of ligated linkers prior to PCR and teaches that the solution to that problem is to remove unligated linkers by gel filtration (see column 9, lines 1-17).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the nucleic acid selection method of Shagin et al as taught by Birkenmeyer et al (U.S. Patent 6,455,255) since Birkenmeyer teaches "In partial response to the adapter set carryover problem described above, all restriction enzyme digests were purified by passaging these digests through a gel filtration spin column prior to ligation of a new adapter set. It was believed that this would greatly reduce the concentration of free adapters cleaved off by the restriction enzyme, thus preventing them from participating in the subsequent ligation reaction. Furthermore,

during the initial generation of driver and tester amplicons, spin column purification was used to reduce the level of non-ligated oligonucleotide set #1 so that it would not compete with the selective PCR primers. Finally, it was thought that spin column purification would help to eliminate very small PCR products, such as primer dimers, which can out-compete the larger desired products (see column 9, lines 1-17). So an ordinary practitioner would have been motivated to use gel filtration in order to avoid the problem recognized by Birkenmeyer that when PCR is performed after linker ligation, the linkers may compete with the PCR primers. Using gel filtration to remove the unligated linkers as taught by Birkenmeyer would avoid this problem so that the linkers will not compete with the PCR primers. This would motivate the ordinary practitioner to use the same solution in the linker ligation followed by PCR amplification method of Shagin since the same competition problem would occur and the same solution would resolve this problem.

Response to Arguments

9. Applicant's arguments with respect to the claims have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JEFFREY FREDMAN
PRIMARY EXAMINER
1/1/09